REMARKS

In the Office Action dated May 15, 2003, claims 30-41, in the above-identified U.S. patent application were rejected. Reconsideration of the rejections is respectfully requested in view of the above amendments and the following remarks.

Claims 30, 31, 35, 36 and 41 were rejected under 35 USC §102(e) as anticipated by Lee in view of Lodish. Lee discloses a sequence corresponding to amino acids 387-501 of SEQ ID NO:2 which is a fragment of the mature protein as disclosed in the present application. Claim 30 has been amended to indicate that the nucleotide sequence encodes a mature protein including amino acids 382-501 of SEQ ID NO:2. These amino acids are encoded by nucleotides 1783-2142 which are recited in part (b) of claim 30.

In addition, attached to this response is a copy of an article, Özkaynak et al., J. Biol.Chem 267 (1992), which indicates that the mature protein occurs by proteolytic cleavage immediately past RXXR and that the mature protein is not formed by any random fragment (see page 25222, regarding *"Proteolytic Maturation Sites in the Pro-domain - The proteolytic cleavages resulting in removal of pro-regions from the mature proteins occur immediately past the sequence RXXR in members of this family").* This article also states that *"Comparison of 16 examples shows that these RXXR sites are typically followed by serine or alanine. On occasion, RXXR is followed by aspartic acid, glycine, or glutamine."* Thus, the first processing site of MP52 and GDF-5 fulfills all requirements for a site to be cleaved efficiently by proteases, it complies with the RXXR rule and starts with alanine (amino acid 382). In contrast to this, Lee discloses an additionally assumed cleavage site KR. This is only a dibasic

cleavage site, which would additionally generate a protein (110 amino acids) which would start with an untypical proline. Though Lee indicates that his protein is a mature protein, Lee only discloses possible cleavage sites for the mature protein, he does not show that the less likely "KR" site is actually used. In the case of MP52, the site coinciding with the RXXR rule is used, i.e. the RRKRR site. Hötten et al, Growth Factors, 1996, discloses that the cleavage of the mature MP52 is only effected at the typical RRKRR site. However, as known, not only the mature protein with the typical Ala is produced, but also the protein with the additional Arg, depending on the cell line used for the expression, as the sequence RRKRR contains two possible RXXR (RRKR and RKRR) sites. In view of these references, one skilled in the art would understand a mature MP52 protein to be what is actually produced during expression or what would be expected due to the known RXXR rule (i.e. a 120 or possibly still 121 amino acid protein) and not, what Lee predicted (110 amino acids), which could not be evidenced. Hence, for a person skilled in the art the protein produced after processing at the typical RRKRR site is the mature protein. The above discussed alternative mature protein, having an additional arginine before the alanine, is not comprised by the present application since according to the present application, the mature MP52 is produced after nucleotide 1782.

Also attached to the present response, is an article by Sanyal et al (2000), wherein Figure 2 shows an alignment of amino acid sequences of mouse-,rabbit- and human MP52 (it was found that mature rabbit is 100% identical to MP52). The subtitle of the figure states that "*The polybasic processing site is indicated by a box and the site of cleavage by which mature GDF5 is generated is indicated by an arrow.*" Thus, Sanyal also indicates that mature proteins start with alanine to achieve the 120 amino acid mature MP52.

Sanyal also states on page 207 that "*The presence of a polybasic processing site (a sequence at which the precursors of the TGF- superfamily of proteins are cleaved) and seven cystein residues (characteristic of bioactive forms of the TFG- superfamily) demarcate the mature portion of rbGDF5*". Thus, Sanyal indicates that the mature protein is clearly demarcated by the polybasic cleavage site as described in the present application and not by the dibasic KR site as disclosed in Lee. In view of the above amendments and arguments, applicants request that this rejection be withdrawn.

Claims 30, 32-34, and 37-40 were rejected under 35 USC §103(a) as obvious over Lee in view of Lodish and Oppermann. As discussed above, Lee does not disclose or suggest a nucleotide fragment which encodes the mature protein with amino acids 382-501 according to SEQ ID NO:2. The office action indicates that one skilled in the art would have used GDF-5 due to its homology with BMPs, in order to obtain cartilage-and bone inducing properties in a bioassay, in view of Oppermann. Though GDF-5 shows some homology with BMPs, it forms an individual subfamily together with GDF-6 and GDF-7, which is clearly different from the BMP2/BMP4 sub-group (see Figure 4 in Lee, US 5,801,014). Furthermore, Lee himself states in column 14, from line 17: *"Also the C-terminal portion of GDF-5 clearly shows homology with the other family members, the sequence of GDF-5 is significantly diverged from those of the other family members (FIGS. 3 and 4)".* Hence, the skilled person could not reasonably predict a cartilage- and bone inducing effect just because of some homology with another sub-family like BMP-2 and BMP-4. Though there are effects which can be found in different subfamilies, there are also differences in the modes of action. Even within a subfamily there are still differences. Therefore, it would not have been obvious that the GDF-5/6/7 subfamily would have the same cartilage-and bone inducing action as BMPs. Applicants point out that in the

priority document Lee does not explicitly describe the influence of GDF-5 on the skeletal system (e.g. cartilage and bones), he generally states that *"GDF-5 may have similar activities and may be useful in repair..."*). Applicants point out the following parts of Lee, US 5,801,014: col. 2, lines 1-2 "*and those in involving skeletal system*"; col. 2, Figure 5 and 6; col. 3, paragraph lines 22-41; col. 8, lines 6/7;" or skeletal system (e.g. bone, cartilage); EXAMPLE 3, and EXAMPLE 4, and point out that no claims contained in the priority document refer to cartilage or bones. It appears that Lee initially took the activity of GDF-5 in the cartilage/bone region (skeletal system) for granted, and later detected expression of GDF-5 in the skeletal system (limb mesenchym of mice embryos, see Example 3) and observed activities in the skeletal system of transgene mice (bone induction) (Example 4) after the date of the priority document and the present application. If it had been obvious for a skilled person to detect such a bone inducing activity, Lee would have stated this in the priority document and would have acknowledged such activity in the claims. At the priority date, Lee was a known expert concerning the TGF- superfamily, he had earlier detected the protein GDF-1 (e.g. PNAS 88, 1991, see D13 in 20883E EP or Lee, Mol. Endocrinol., 1990). Hence, it was not immediately obvious to a recognized expert in the field of the TGF- superfamily, like Lee, to combine GDF-5 with matrices which are used for BMPs, as it was not clear at all to an expert, if a BMP-similar activity could reasonably be expected based only on homologies detectable at the priority date. It would have been impossible to infer with high expectations of success, the same activity and possibility of combination with the same matrices in pharmaceutical compounds based only on certain homologies; there are other indications required. BMP-3, for example, only purified from bone, initially was accrued a typical cartilage-and bone induced activity in agreement with the expectations. Later, it was found that the cartilage-and bone inducing activity of this

recombinant material could not be confirmed and BMP-3 has been ascribed a rather antagonistic part concerning the skeletal system, even though it has homologies with BMP-2 and BMP-4, as cited by the Examiner (see D24 and D32(No. 1 Bahamonde & Lyons) in 20883E EP). Therefore, cartilage-and bone inducing activity clearly cannot be predicted based only on homology with BMPs as suggested in the office action and the presently claimed invention would not have been obvious in view of the cited prior art. In addition, applicants point out that the prior art does not suggest or disclose the angiogenesis activity of the presently claimed protein.

Claim 38 was rejected under 35 USC §112, second paragraph as indefinite. Claim 38 has been amended as suggested in the office action to recite "a matrix". In view of this amendment, applicants request that this rejection be withdrawn.

Applicants respectfully submit that all of claims 30-41 are now in condition for allowance. If it is believed that the application is not in condition for allowance, it is respectfully requested that the undersigned attorney be contacted at the telephone number below.

In the event this paper is not considered to be timely filed, the Applicant respectfully petitions for an appropriate extension of time. Any fee for such an extension together with any additional fees that may be due with respect to this paper, may be charged to Counsel's Deposit Account No. 02-2135.

RESPECTFULLY SUBMITTED,					
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Enclosures: Sanyal et al., Molecular Biotechnology, Vol. 16, 2000
Özkaynak, et al., J. of Biol.Chem., Vol.267, No. 35, 1992